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The impact of diet-based glycaemic response and glucose regulation on cognition: evidence across the lifespan.

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Abstract

The brain has a high metabolic rate and its metabolism is almost entirely restricted to oxidative utilization of glucose. These factors emphasize the extreme dependence of neural tissue on a stable and adequate supply of glucose. Whereas initially it was thought that only glucose deprivation (i.e. under hypoglycaemic conditions) can affect brain function it has become apparent that low-level fluctuations in central availability can affect neural and consequently, cognitive performance. In this paper the impact of diet-based glycaemic response and glucose regulation on cognitive processes across the life span will be reviewed. The data suggest that although an acute rise in blood glucose levels has some short-term improvements of cognitive function, a more stable blood glucose profile which avoids greater peaks and troughs in circulating glucose is associated with better cognitive function and a lower risk of cognitive impairments in the longer term. Therefore, a habitual diet that secures optimal glucose delivery to the brain in the fed and fasting states should be most advantageous for the maintenance of cognitive function. Although the evidence to date is promising, it is insufficient to allow firm and evidence-based nutritional recommendations. What limits our ability to draw strong conclusions from the findings of previous studies is the fact that they often differ widely with respect to subject characteristics and cognitive tests used. Future research needs to carefully consider conceptual and methodological factors including potential inter-individual differences, adequate selection of tests and control of extraneous (confounding) variables. The rise in obesity, diabetes and metabolic syndrome in recent years highlights the need for targeted

dietary and lifestyle strategies to promote healthy lifestyle and brain function across the lifespan and for future generations. Consequently, there is an urgent need for hypothesis-driven, randomised controlled trials that evaluate the role of different glycaemic manipulations on cognition.

Background

Rise in nutrition-related illness highlights the need for targeted health promotion and interventions across the lifespan and for future generations. Traditionally the focus of such interventions was on development of chronic disease and premature death. However, there is now a large body of evidence demonstrating that cognitive decline accompanies certain metabolic health conditions such as type 2 diabetes, metabolic syndrome and obesity and that modifiable lifestyle factors including diet may contribute significantly to the risk of cognitive decline, including dementia[1]. Consequently, there has been increasing interest in the effects of nutrition on cognitive performance and more specifically how cognitive performance can be optimised using nutritional interventions. When looking across the life-span, broadly speaking nutritional interventions offer opportunity to i) optimize cognitive development during infancy and childhood, ii) ensure the highest levels of cognitive function during adulthood and iii) prevent cognitive decline in older age (see Figure 1).

The macronutrient glucose is perhaps most thoroughly researched in terms of its effects on cognition. Investigations into the effects of glucose on cognition have served as a useful prototype to develop paradigms for studying the effects of more complex nutrition-like interventions. The notion that oral glucose administration might facilitate mental performance was first proposed in the 1950's. Hafermann[2]investigated the effects of glucose administration on school children, and observed a distinct increase in cognitive performance, including performance in mathematics and generally improved concentration. However, it was not until the mid 1980's that glucose effects on cognitive performance became more widely investigated[3]. Here the impact of diet-based glycaemic response and glucose regulation on cognitive processes across the life span will be reviewed. Before considering the relationship of glucose, glycaemic response and cognitive processes, some features of glucose metabolism important for the understanding of its role in cognition will be discussed.

Glucose: the major source of energy for the brain

The central significance of glucose as the major nutrient of the brain, its metabolism and control, have been well documented. All processes of cells (including nerve cells) require energy. In humans and most animals, adenosine triphosphate (ATP) works as the main carrier of chemical energy. The human body uses three types of molecules to yield the necessary energy to drive ATP synthesis: fats, proteins, and carbohydrates. In addition to being the major source of biological energy, aerobic carbohydrate metabolism is the main source of energy available for brain tissue and glucose and oxygen are the sole metabolic energy source that can cross the blood brain barrier and hence be utilized by brain cells to form ATP[4]. Brain tissue is absolutely dependent upon the oxidative metabolism of glucose for energy as glucose is essentially the sole energy fuel for the brain except during prolonged starvation when ketone bodies, generated by the liver, replace glucose[5]. Associated measurements of oxygen and glucose levels in blood sampled upon entering and leaving the brain in humans show that almost all the oxygen utilised by the brain can be accounted for by the oxidative metabolism of glucose[6]. Compared with other organs, the brain possesses paradoxically limited stores of glycogen, which without replenishment are exhausted in up to 10 minutes. In nervous tissue, glycogen is stored in astrocytes. Astrocytes participate significantly in brain glucose uptake and metabolism and due to their location and metabolic versatility; they may be the “fuel processing plants” within the central nervous system[7] . Due to limited glycogen storage capacity, the brain relies on a continuous supply of glucose as its primary fuel, delivered via the bloodstream. The entry of glucose into the brain is mediated by the family of glucose (GLUT) transporters which are adapted to the metabolic needs of the tissue in which it is found. The primary GLUT isoforms in the brain are GLUT1 and GLUT3 but others have been detected in different brain regions, at a lower level of expression[8].

The immense expenditure of energy by the brain relative to its weight and volume is thought to be due to the need to maintain ionic gradients across the neuronal membrane, on which the conduction of impulses in the billions of neurons. In addition, there is no break from the brain’s energy demand as the rate of brain metabolism is relatively steady day and

night, and may even increase slightly during the dreaming phases of sleep. Thus the energy requirements of brain tissue are exceptionally constant[9] and glucose deprivation can severely disrupt neuronal activity, producing EEG patterns characteristic of lowered cognitive functioning[10]. Indeed, when blood glucose drops below 4 mmol/l (72 mg/dl; hypoglycaemic condition), it can cause discomfort, confusion, coma, convulsions, or even death in extreme conditions[11]. Conversely, persistent blood glucose concentrations above the normal range (hyperglycaemic condition) can also have damaging physiological effects. Because glucose exerts osmotic pressure in the extracellular fluid, extremely high blood glucose concentrations can cause cellular dehydration. An excessively high level of blood glucose concentration also causes loss of glucose in the urine, which can affect kidney function and deplete the body's supply of fluids and electrolytes[12].

Glucose brain metabolism: changes across the lifespan

The rate of glucose brain metabolism changes across the life span. Initially, there is a rise in the rate of glucose utilization from birth until about age 4 years, at which time the child's cerebral cortex uses more than double the amount of glucose compared to adults. This high rate of glucose utilization is maintained from age 4 to 10. Childhood is a time of intense learning and therefore coincides with the most metabolically expensive period[13]. The high energy demand of a child's brain requires the use of the majority of hepatically generated plasma glucose[14]. In addition, glucose supply needs to be particularly stable as impairments are thought to occur at higher plasma glucose level (4.2 mmol/l)[15]. After this period, there is a gradual decline in glucose metabolic rate, reaching adult values by age 16-18 years (see for example[16]). This is followed by a plateau phase until middle age after when a significant age-related decline in cerebral glucose metabolism can be observed (see for example[17]). This age-specific metabolic pattern of glucose consumption has not been observed in other species and it has been argued that this could be a driver or indeed a consequence of human cognition[18].

Most children and young adults maintain circulating glucose within the normal range throughout cycles of feeding and fasting and balanced alterations in secretions of regulatory hormones. In contrast, older adults have a broader range over which circulating glucose is maintained and in addition have attenuated counter regulatory responses. Circulating

insulin levels tend to be elevated with age (approx. 8% higher than in young adults) and are indicative of reduced insulin sensitivity[19]. Reduced insulin sensitivity or insulin resistance is a condition where individuals develop resistance to the cellular actions of insulin, characterized by an impaired ability of insulin to inhibit glucose output from the liver and to promote glucose uptake in fat and muscle. Both effects of insulin insensitivity on liver and muscle tissue cause elevations in peripheral blood glucose levels. Changes in insulin action have been observed at different stages of the development. Basal insulin secretion increase during puberty, falling back to pre-pubertal levels in adulthood[20]. Yet, fasting glucose levels remain constant, implying an increase in tissue resistance to insulin coinciding with puberty[21]. The reason for the puberty-induced reduction of insulin sensitivity appears to be growth-hormone related[22-24]. Growth hormone secretion reaches a peak at around puberty and will begin to decrease by the age of 21 years[25]. It is commonly in middle age where insulin resistance and poor glucose tolerance become a health issue. Given that the brain uses glucose as a primary substrate for brain function, it is perhaps not surprising that conditions that affect peripheral and central glucose regulation and utilization may also affect cognitive functioning. Moreover, based on the evidence above there might be 'critical periods' in which alterations in cerebral glucose supply might have more pronounced effects on cognitive performance.

The consequences of fluctuations in central glucose availability have begun to be better understood. Whereas initially it was thought that only glucose deprivation (i.e. under hypoglycaemic conditions) can affect brain function it has become apparent that low-level fluctuations in central availability can affect neural and consequently, cognitive performance. In the next section we will review work into the phenomenon of cognitive enhancement following a glucose load.

Acute administration of a glucose load: prototypical experimental paradigm

Over the last thirty years, a large body of literature has demonstrated beneficial effects of acute glucose administration on cognition in various populations (for reviews see [26, 27]). The general methodology used in these studies involves administration of an oral glucose load (usual range between 25 and 50g of glucose) after a period of fasting (ranging from 2h to

overnight fast) followed by assessment of cognitive performance and measurement of capillary blood glucose levels.

Using this experimental paradigm, beneficial effects have been observed across different populations. For example, glucose administration has been shown to enhance cognitive performance in adolescents[28], young adults[29-38], older adults[39, 40] and improvements have been observed in subjects with mild or severe cognitive pathologies, including individuals with Alzheimer's disease and Down's syndrome (see [26, 27] for reviews). In addition, facilitation of cognitive performance induced by elevations in plasma glucose levels has also been reported in patients with schizophrenia[41, 42]. It is important at this point to note that these results do not reflect a negative effect of fasting on cognition and memory, as the degree of fasting in which participants engaged was not exceptional and participants do not reach blood glucose levels associated with hypoglycaemia. What these findings demonstrated are the beneficial cognitive effects of raising blood glucose levels within normal physiological limits.

Cognition is not a monolithic concept, but encompasses a range of mental processes which occur when information is perceived, evaluated, stored, manipulated, retrieved or otherwise processed. Important components of cognition are perception, attention, vigilance, memory, executive function and language. These can be measures using different task which in turn allow assessment of subcomponents. In terms of cognitive tasks affected, benefits have been found to occur in a range of cognitive domains, including information processing and attention[39, 43-46], working memory[29, 30, 35, 36, 47], executive function[48, 49] problem solving[50] and long-term memory[29-31, 33-35, 51-53].

Trying to define the various aspects of cognition, which are most receptive to glucose-induced enhancement, the clearest enhancement effects of increased glucose supply have been observed for verbal declarative long-term memory over a variety of conditions and paradigms (for review see[54]). As different aspects of cognition pertain to different neural structures and network, this allows speculation about the areas of the brain that might be particularly susceptible to glycaemic fluctuations. The robust effects on long-term memory, suggest that glucose facilitation may be particularly pronounced in tasks that pertain to the

hippocampal formation[29]. The level of task demand is a further moderating factor for cognitive enhancement by increased glucose availability. Indeed, in younger participants, glucose-related improvement of cognition appears to be related to the difficulty of the cognitive tasks. Tasks which are more cognitively demanding appear to be more sensitive to the effect of glucose loading[30, 36, 55]. In addition, 'depletion' of episodic memory capacity and/or glucose resources in the brain due to performing a concomitant cognitive task might be crucial to the demonstration of a glucose facilitation effect. The reason for this is likely to be that younger individuals already working at optimal physiological and cognitive efficiency (and therefore functioning at or near a ceiling level of performance), whereas older participants and clinical patients are unable to achieve optimal performance due to age- or illness-related degenerative changes.

Indeed, while both young and older adults show cognitive improvement after the oral administration of glucose, the effects appear to be more profound in older individuals. Cognitive decline over the aging process has been well documented[56-58]. Traditionally, cognitive impairments are assumed to reflect deficits caused by damage of brain areas or systems in which cognitive processing in normal subjects occurs. However, more recently there has been a focus shift on specific physiologic and metabolic impairments that appear to contribute to the cognitive decline observed in ageing. Older adults have a broader range over which circulating glucose is maintained and in addition have attenuated counter regulatory responses. These suboptimal metabolic and cognitive conditions are likely to make older individuals more susceptible to glucose facilitation of cognitive performance.

The energy cost for effortful, controlled or executive processes appears to be significantly higher than that for automatic or reflexive processes[59]. Effortful, controlled or executive processes are processes that are reliant on the central executive, in which thoughts, behaviours and actions are coordinated to allow goal directed and purposeful behaviour[60], while automatic and reflexive behaviours are evolutionarily predisposed or learned behaviours elicited by environmental stimuli. Indeed, lowered peripheral glucose levels following performance of a cognitively demanding task have been reported[55, 61]. This fall in plasma glucose could reflect a more efficient transfer of glucose to the brain which in turn results in increased provision centrally. One should be cautious when making assumptions

about peripheral blood glucose levels and their putative effects on the brain, as other studies have failed to demonstrate such findings[62, 63]. Nevertheless, the evidence suggests that cognitively demanding tasks and in particular those relying on executive functions are also sensitive to changes in glucose (see for example[59, 64]) Administration of a glucose drink would consequently provide the brain with sufficient metabolic resources for extensive cognitive processing and support the brain areas under greatest cognitive load, and thus lead to improved performance.

Apart from task difficulty and cognitive domain, the amount of glucose administered is also an important factor. As with many substances affecting cognitive performance, glucose displays an inverted U-shaped dose-response curve, and its effect is time dependent[3]). For older adults 25g of glucose appear to be the optimal dose, with performance deterioration observed after administration of 75g of glucose[65]. For young adults 25g also seems to most reliably facilitate cognitive performance, however, there is evidence suggesting that the optimal dose or shape of the dose-response curve may be dependent on inter-individual difference in glucose metabolism, and the cognitive domain being assessed[33]. Of note, the cognitive enhancing effects of pharmaceutical substances such as stimulants (methylphenidate, modafinil) and acetylcholinesterase inhibitor (dementia drugs) in healthy individuals are generally moderate or small (as estimated by Cohen's d effect size) according to systematic reviews (see for example[66, 67]). The effects of glucose administration are comparable with those from pharmaceutical interventions, with effect sizes for glucose effects range from 0.34 to 4.26, with typical values of 1.02, 0.81 and 1.07 for heavily loaded working memory and verbal episodic recognition and recall respectively[68].

Glucose facilitation of cognitive performance: putative underlying mechanisms

The precise mechanisms by which increased peripheral and/or central glucose availability affects cognitive processes are still unclear. There are two broad theoretical approaches: energetic demand models and domain specific models. Energetic demand models, have their basis in the observation that the amount of mental effort involved in cognitive processing is an important determinant of a task's susceptibility to glucose enhancement. Domain specific theories, on the other hand stipulate that certain areas of the brain are more susceptible to changes in glucose availability. However, as will become clear these

different approaches are by no means mutually exclusive, their relative explanatory value depending on cognitive task and brain structure.

Glucose metabolism varies throughout tissue/cell types of the brain, with a clearly established correlation between increased energy metabolism and increased neuronal activity and energy metabolism[69].Both the rate of blood to brain glucose transport[70] and glucose metabolism[71] are stimulated in different areas in the brain during cognitive tasks relevant to that area. There is evidence that performing cognitively demanding tasks increases total brain consumption by as much as 12%[72].

As described, glucose exerts quite robust effects on long-term memory tasks. The hippocampus is the brain region most strongly implicated in long-term memory performance[73]. Microdialysis measurements of brain glucose have shown a large decrease in hippocampal extra cellular fluid (ECF; 32 $\pm$ 2%) in rats tested for spontaneous alternation on a four-arm maze (a difficult memory task), while a smaller decrease (11 $\pm$ 2%) was seen in rats tested on a simpler three arm- maze, suggesting that the changes observed in ECF glucose are related to task difficulty. The fall in ECF can be prevented by administration of glucose, which in turn leads to enhanced memory performance[74]. There is some evidence that the concentration of extracellular glucose in the brain after its transfer across the blood-brain barrier from plasma glucose varies with brain region from 1.3 mmol/l in the hippocampus to 0.3-0.5 mmol/l in the striatum (for review, see[75]). These findings suggest that the hippocampal area is particularly sensitive to energy fluctuations. However, the hippocampus has relatively greater glycogen stores compared to other areas suggesting that it has evolved some protection against temporary deficits (13 mmol/l compared to 5-6 mmol/l in the cerebral cortex[76].

Research also shows that difficult tasks are more likely to be susceptible to glycaemic interventions. Difficult tasks include those involving executive functions pertaining to frontal brain regions: inhibition/self-control, working memory and mental flexibility[77, 78]. Evidence suggested that tasks that demand such cognitive control and attentional resources appear to be more energy demanding[59]. Consequently, another area of the brain which appears to be particularly sensitive to energy fluctuations is the frontal cortex. The cerebral cortex, and in particular the prefrontal cortex, represents the neural basis of higher cognitive functions

e.g[79, 80]. Aspects of higher-level cognition were probably one of the last cognitive abilities to develop ontogenetically. Based on the "last-in, first-out rule", cognitive abilities that developed last ontogenetically are likely the first to become impaired when cognitive and/or physiological resources are compromised. Consequently, optimal performance on task pertaining to function of the pre-frontal cortex might require more energetic fuel than others.

From an evolutionary perspective, energy mobilization is of particular importance in times of stress in order to prepare the body for the "fight or flight" response. Exposure to threats or stressors results in activation of two major endocrine systems, the hypothalamic-anterior pituitary-adrenocortical axis (HPA) and the sympatho-adrenomedullary axis (SAM axis). A major physiological role of activation of both endocrine systems is considered to be a temporary increase in energy production and more specifically provision of additional metabolic fuel through increase in glucose availability[81]. Liberation of additional metabolic resources allow the organism to adapt rapidly to such environmental challenges.

From a memory perspective such endogenous processes could act as relevance moderators of the "print-now" signal by regulating encoding and synaptic plasticity[82]. That is to say they could moderate memory strength and contribute to memory formation by selectively promoting the storage of significant events and not trivial ones[83, 84]. In terms of its influence on prefrontal cortex function, these processes could moderate energy supply, allowing allocation of optimal resources to functions relevant to survival. Administration of a glucose load might by-pass the above mentioned endocrine activation and the concomitant increased peripheral and/or central glucose availability could lead to optimal energy supply.

Glucose has other important mechanisms of action in the central nervous system, including interactions with various neurotransmitter systems (e.g. acetylcholine, dopamine, opiates). There is evidence suggesting that the cognitive facilitation observed after glucose loading is due to an increase in enhancement of acetylcholine synthesis and/or release (see[26] for review). However, effects on neurotransmitter systems and energy supply theories are not mutually exclusive. For example, Peters et al.[85] proposed a model for brain energy supply

controlled by high-affinity and low-affinity ATP sensitive potassium channels in neocortical neurons. According to the model, high-affinity ATP sensitive potassium channels are located on excitatory neurons, whereas those with low-affinity are located on inhibitory neurons. Occupancy of these channels changes depending on ATP levels whereby low (but not critically low) ATP concentration would lead to excitatory glutamatergic neuronal activity, whereas at high ATP levels a shift towards predominately inhibitory GABA-ergic neuronal activity occurs[85]. Moreover, Sandberg et al[82] described a model of an autoassociative network with plasticity modulation that produced an inverted U-shaped curve to overall plasticity similar to the one commonly observed in arousal-performance or glucose dose-response plots. Additional energy availability could result in optimal neuronal activation as defined by optimal balance of inhibitory and excitatory activity which in turn results in peak cognitive performance.

In addition, elevated insulin in response to hyperglycaemia rather than glucose levels *per se* may moderate memory performance (see[86] for review). Originally, insulin was considered only as a peripheral hormone, unable to cross the blood-brain barrier (BBB) and to affect the central nervous system (CNS). However, there is now increasing evidence that neuronal glucose metabolism is antagonistically controlled by insulin and cortisol (see[87, 88] for reviews). Insulin present in adult CNS is primarily derived from pancreatic β-cells and is transported by CSF into the brain. It is also partially formed in pyramidal neurons, such as those in the hippocampus, prefrontal cortex, entorhinal cortex and the olfactory bulb, but not in glial cells[89]. The suggestion that glucose administration and/or impairments in glucoregulatory mechanisms exert the most profound effects on medial temporal regions is supported by functional characteristics associated with these areas such as high density of insulin receptors in the hippocampus (e.g. [90, 91]) which are known to promote cellular glucose uptake (e.g. see [26, 92]). Insulin-sensitive glucose transporters such as GLUT4 (which mediate passive diffusion of glucose through the blood brain barrier) are also enriched in the hippocampus (though the highest concentration is in the cerebellum, see[93]. Given the established role of the hippocampus in memory, elevated insulin in response to hyperglycaemia may boost glucose utilization in the hippocampus and result in improved performance[94]. Indeed, at the molecular level, insulin and/or insulin receptors seem to contribute to the regulation of learning and memory via the activation of specific signalling

pathways, one of which is shown to be associated with the formation of long-term memory (for a more detailed account see [95, 96].

Lastly, glucose might also act via peripheral physiological mechanisms, which in turn facilitate central mechanisms involved in cognition. It has been suggested that important players in this peripheral route are the liver and the vagus nerve. Messier and White [97, 98] suggested that changes in cell membrane transport in the liver following administration of high doses of glucose and fructose (> 1000mg/kg) are detected by the coeliac ganglion, then transformed into neural signals and finally carried via the vagus nerve to the brain. In accordance with this suggestion, coeliac ganglion lesions (which block most of the efferents of the liver) have been shown to abolish the mnemonic effect of glucose[98]. To date there is no concrete information available concerning how this proposed neural signal from the liver might influence cognitive performance when it reaches the brain. However, the nucleus of the solitary tract (NST) in the brain stem is the main relay station for afferent vagal nerve fibers. This nucleus has widespread projections to numerous areas in the cerebral cortex, including the hippocampus and the prefrontal cortex and stimulation of the vagus nerve induces changes in the electrophysiological and metabolic profile of these brain structures[99]. The research is not yet conclusive, but suggests that the underlying mechanism is multifarious. The most likely scenario is that glucose provides additional metabolic fuel under high demand conditions and that certain areas of the brain are more susceptible to limitations in fuel supply, or are evolutionarily programmed to react to an endogenous rise in plasma glucose levels.

Glycaemic regulation and cognition

The investigations into the effects of administration of a glucose load have been important in elucidating the potential underlying mechanisms. Acute administration of a glucose load has been shown to benefit cognitive performance. This can be advantageous in conditions where there is a need for fast 'fuel refill', for example in situations of stress combined with physical performance (see e.g.[100]). However, over longer time periods, elevated blood glucose levels act as an allostatic load to biological system and can accelerate disease processes. Due to the complex relationship between glucose administration, glucose metabolism and cognition, inducement of repeated hyperglycaemic conditions would

eventually result in performance decrements as it affects glycaemic regulation, i.e. the ability of the body to effectively regulate blood glucose levels and to remove glucose from the blood. Blood glucose levels of healthy individuals respond to glucose ingestion by rising for roughly half an hour and then returning to near baseline measures within 2 hours, whereas in individuals with poor glucose tolerance, blood glucose levels commonly peak quickly and then fall more slowly.

Impairments in glucose and insulin regulation lead to increases in plasma glucose levels, but decreased glucose utilization due to insulin resistance. Given the dependence of the brain on glucose for optimal functioning and the evidence showing that acute glucose administration can influence cognitive function it is not surprising that impaired glycaemic control may contribute to cognitive impairments (see[101] for a review of the literature). Consequently, in addition to food intake, glycaemic control is another important factor when considering cognition across the life-span. Conditions in which glycaemic regulation is severely compromised are diabetes type 1 and type 2, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG). Cognitive impairments were indeed one of the earliest recognized neurological complications associated with diabetes[102]. To date, numerous studies have compared cognitive functioning in diabetic patients with non-diabetic controls[103]. Although these studies differed widely with respect to patient characteristics (age, duration and type of diabetes) and cognitive tests used, the majority of these studies demonstrated cognitive impairments in this population which included decreased performance on various attention and memory tasks[101, 104-107]. Risk factors associated with cognitive complications in diabetes appear to be i) degree of metabolic control[108] and ii) repeated episodes of hypoglycaemia[109]. It is therefore not surprising that in children diagnosed with Type 1 diabetes before age 10 years, cognitive complications are generally only observed if they have a history of hypoglycaemic seizures[110]. It is evident from the literature that Type 2 diabetes is the metabolic condition associated with an increased risk of cognitive dysfunction[111-113].

However, there is now increasing evidence of a relationship between glycaemic control and cognitive functions in healthy, non-diabetic populations (see [101, 105] for reviews). As mentioned earlier, impairments in glucose tolerance become a larger issue in middle age

and consequently it is likely that the negative cognitive impact of abnormalities in glucose tolerance increases with age. Cognitive decline over the aging process has been well documented and it has been suggested that normal aging may represent a condition in which there is greater vulnerability to disrupted glucose regulation (see for example[58]). Indeed, evidence to support this hypothesis is provided by the finding that memory performance in elderly participants with poor glucose regulation is impaired relative to elderly participants with good glucose regulation[114-116]. Moreover, age-related changes in glucose metabolism have been identified as a risk factor for Alzheimer's disease [26, 86, 117]. Consistent with this notion is the finding that hyperglycaemia (induced through oral and intravenous glucose administration) can facilitate memory performance in Alzheimer's patients, at least in the early stages of the disease[118]. Interestingly, alterations in blood glucose regulation seem to depend on the severity of the disease process. More specifically, high insulin levels are observable at the very early ('very mild') stages and decline as dementia progresses. Moreover, memory facilitation can be achieved through glucose administration in the early stages and the degree of facilitation decreases at more advanced stages of the disease[94]. Indeed, as abnormalities in brain insulin resistance and deficiency have been observed in Alzheimer's disease, and the fact that molecular and biochemical hallmarks of Alzheimer's disease, such as neuronal loss, synaptic disconnection, tau hyperphosphorylation, and amyloid-beta accumulation overlap with Type 1 and Type 2 diabetes, the term "Type 3 diabetes" has been suggested to account for the underlying abnormalities associated with AD-type neurodegeneration[119].

However, and perhaps more worryingly, performance decrements due to poor glucose regulation have been reported in younger individuals (see [101, 105] for reviews). For example, recent studies have shown that even in a healthy young student population those with better glucose regulation (those who had the smallest blood glucose rise following glucose ingestion) perform better on tests of memory[35, 49, 105, 120-122], vigilance[49, 120], planning[120] and dichotic listening[123] compared to those with poorer glucose regulation. In addition, glucose administration preferentially improved performance in those with poorer glucose regulation and the effects are less likely to be observed in good glucose regulators in both old and young populations[26]. This would suggest that glucose control or tolerance is associated with cognition throughout the lifespan. Overall there appears to be some

evidence that glucoregulation may exert direct effects on cognitive function in that those with poor glucoregulation may demonstrate mild cognitive deficit compared with good glucoregulation. However, research in young adults is limited, furthermore the methodologies for determining glucoregulatory control have been varied. Only a few studies have used a standardized oral glucose tolerance test (OGTT) for the evaluation of glucose tolerance in healthy young adults (for example [35, 124]). The OGTT involves administration of a 75g glucose load after a minimum eight hour fast and is the gold standard test for the diagnosis of diabetes mellitus (WHO, 1999). Moreover, the majority of studies have only assessed one specific measurement of glucose tolerance. Several glucoregulatory indices have been previously evaluated for their relationship with cognitive performance in younger and older participants. These include: fasting levels, peak glucose levels, recovery and evoked glucose to baseline levels and incremental area under the curve (AUC) (see[35]). At a younger age, the deficits associated with poor glucoregulation may be minimal and hard to detect therefore it is important to identify the most sensitive marker. A study in our laboratory found AUC, which takes baseline blood glucose levels into account (AUC with respect to ground; see[125]

for calculations), to be the best predictor of cognitive performance, whereas the most commonly used incremental AUC did not show a strong association[35]. This suggests that overall circulating glucose levels may be an important factor in the assessment of glucoregulation in sub-clinical; populations with normal glucose tolerance as defined by the World Health Organisation (WHO). Indeed, a recent study identified fasting blood glucose levels as a predictor for cognitive performance[126]. Young adults who were obese but otherwise healthy had higher fasting glucose levels compared with normal weight participants. In addition, higher glucose levels were associated with poorer cognitive performance on tests of inhibitory control, especially among individuals with pre-diabetic levels. Consequently, subclinical elevations in blood glucose may contribute to cognitive impairments before the development of clinically defined disease states.

The postprandial glycaemic response and cognition

When considering the nature of glucose availability, the rate at which food increases and maintains blood glucose, i.e. 'the Glycaemic Index' (GI) appears to be an important modulating factor. Shortly after intake of a high GI food there is a relatively rapid rise in blood glucose levels followed by a corresponding rapid decrease, whereas after the intake of a low GI food there is a relatively smaller rise in blood glucose followed by more stable blood glucose concentration. GI solely provides a measure of carbohydrate quality[127], whereas glycaemic load (GL) takes into account the amount of carbohydrates consumed and is calculated by multiplying the amount of available carbohydrate in a food item by the GI of the food and dividing this by 100[128].

Although the effect of glucose administration has been extensively studied in an acute, short-term context, much remains to be done in order to establish the cognitive effects associated with foods of low or high GI and GL. When looking at effects across the life-span, children may be particularly sensitive to glycaemic effects on brain activity and associated cognitive outcomes. As outlined previously, the reason for the greater susceptibility is likely to be due to greater energetic needs during this period compared to adults (see for example[16]) Moreover, it has been suggested that in younger children, the overnight fast induces greater the metabolic stress, as the higher the ratio of brain to liver weight and the greater the metabolic rate per unit of brain weight, the greater the demand on glycogen stores[129] Most studies examining the effects of GI on cognition have focused on the effect of breakfast on children's cognitive performance. It has been shown that children at risk for malnourishment have improved cognition and learning at school if provided with breakfast (see[130] for a review of the literature). Moreover, in developed countries it has been found that skipping breakfast can result in impaired cognitive performance[130, 131]. This suggests that increased plasma glucose availability due to breakfast consumption leads to better cognitive performance. Investigating the optimal rate of glucose supply following breakfast consumption[132], compared a low GI breakfast with a high GI breakfast and found that when children consumed the low GI food they remembered significantly more than when they ate the high GI breakfast. Ingwersen et al[133] compared the cognitive effects of a low GI breakfast and a high GI breakfast across the morning and found that performance on attention tasks was poorer 130 minutes after the high GI breakfast compared to the low GI breakfast. Furthermore, the low GI breakfast prevented a decline in memory performance.

Overall, the results of studies assessing GI in children suggest that a lower postprandial glycaemic response may be protective against a decline in memory and attention throughout the morning[132-139]. However, the evidence is far from conclusive[140, 141] and few studies have actually profiled the glycaemic response in children[142].

From a metabolic perspective, adolescence might also be a time where greater susceptibility to glycaemic variations is observed due to the specific metabolic conditions observed during that time of development. However, few studies have looked at the effects of GI in adolescent populations and the results are somewhat contradictive. Wesnes et al[134] found that a low GI breakfast resulted in better memory performance and attention, but the age range used in this study was quite large (6-16 years). Other studies found performance benefits following a high GI intervention when assessing memory performance[137, 143] whereas a low GI intervention proved to be beneficial for measures of attention/information processing[137]. Cooper et al. (2012) found no difference between high GI and low GI on reaction times, but better performance on an executive function task following low GI[138].

In adult populations, the outcome of investigating the effects of GI has also been somewhat inconsistent. Some show beneficial effects on cognitive performance of low-GI foods[135, 144, 145] whereas others show no such effects [146, 147]. Benton et al[136] compared three breakfasts varying in GL from 2·5 to 17·86 and found that the higher GL foods led to poorer memory performance. Lamport et al[148] investigated the effects of low GI and high GI evening meals followed by a high GI standard breakfast on subsequent cognitive performance. Although no significant differences between evening meals on cognitive performance were observed, the high GI evening meal was associated with better memory performance the following morning after breakfast had been consumed.

To date only a few studies have been carried out into the effect of low GI and GL foods on glycaemic control and cognition in older adults, or populations with pre-existing metabolic and/or cognitive impairments. Kaplan et al. (33) found no differences between meals of different GI in performance in elderly adults. Nilsson, Radeborg and Bjork[144] showed that in a

sample ranging from 49–70 years, performance was better in the late postprandial period after consumption of a low-GI compared to a high-GI breakfast. In adults with type 2 diabetes consuming a low-GI carbohydrate meal, relative to a high-GI carbohydrate meal, has been shown to result in better cognitive performance in the postprandial period[149]. However, two other studies by Lamport et al.[148, 150] did not find any benefits following consumption of a low glycaemic load breakfast. All of these studies investigated the acute effects of postprandial glycaemic manipulation and it may be the case that for these populations cognitive effects will only be evident with chronic improvements in glycaemic control. Indeed, dietary interventions (combined with exercise interventions) have been shown to result in improved cognitive performance in adults with impaired glucose control when they were implemented for 12 months[151].

Overall, it appears that a quick rise in blood glucose levels has some short-term benefits, most notably on memory performance; whereas over longer periods of time (i.e. throughout the morning) a more stable blood glucose profile seems to be more beneficial. In normoglycaemic samples, effects of low GI and/or low GL foods were usually observed in the late postprandial period (75-222 min) where they seem to prevent a decline in attention and memory[132, 133, 135]. In populations with abnormalities in glucose regulation, benefits of low GI foods have been reported in particular following longer-term intervention.

Conclusion

Based on the evidence it is clear that avoiding peaks and troughs in glucose availability is key to optimal cognitive performance. Administration of a glucose load does not represent a viable strategy over any prolonged timeframe since consistently elevated blood glucose leads to insulin resistance. Habitual diets that are rich in refined/simple carbohydrates also lead to high blood glucose. As described earlier, following ingestion of low GI and/or GL food there is a relatively smaller rise in blood glucose followed by more stable blood glucose concentration. Although the evidence to date is promising, there is an urgent need for hypothesis driven, randomised controlled trials that evaluate the role of different glycaemic manipulations on cognition. A relatively recent review into the effects of carbohydrates on cognition in older individuals identified only one study that fulfilled these criteria[152]. The study that was included investigated the acute effects of a glucose drink[153], whereas

studies investigating more complex carbohydrates were not. Future research comparing the effects of different types of carbohydrates, with differing glycaemic profiles are clearly needed. What limits our ability to draw strong conclusions from the findings of previous studies is the fact that they often differ widely with respect to subject characteristics and cognitive tests used. Future research needs to carefully consider conceptual and methodological factors including potential inter-individual differences, adequate selection of tests and control of extraneous (confounding) variables (for a detailed account of methodological issues see [154]).

Moreover, when assessing food items in terms of health benefits and potential dangers, we need to remember that in a habitual diet (as opposed to some of the experimental interventions described earlier), carbohydrates are rarely ingested in isolation. Co-ingestion of other nutrients and nutritional compounds alters the rate of carbohydrate degradation during digestion and consequently affect regulation of postprandial blood glucose and insulin levels. For example, a lowering of glycaemic response has been found when purified extracts of fibre are added to a test food in sufficient quantity [155-158]. Moreover, high fibre diets have been shown to decrease postprandial blood glucose levels[159], improve glycaemic control in diabetic populations and decrease the risk of Type 2 Diabetes[160, 161]. Similarly, dietary proteins have been found to have positive effects on insulin production in populations with normal glucose metabolisms as well as type 2 diabetics[162-164]. Another factor that needs to be considered is the amount and the type of fat consumed. Evidence suggests that the risk of impaired glucose regulation and Type 2 diabetes is associated with a high *trans* fatty acid intake and a low poly-unsaturated to saturated fat intake ratio[165]. There are reports stating that saturated and *trans* fatty acids increase insulin resistance, whereas poly-unsaturated fats decrease resistance and offer protection against disease (see[166]). Consequently, diets high in saturated fats or trans fats should be avoided as they are likely to interfere with glucose tolerance and insulin sensitivity.

In conclusion, a habitual diet that secures optimal glucose delivery to the brain in the fed and fasting states should be most advantageous for the maintenance of cognitive function. This can be achieved by adhering to a low saturated fat and low glycaemic load diet– especially when combined with sufficient physical exercise, which has also been shown to

significantly reduce the risk of developing impairments in glucose metabolism (see for example[167]). This combination of diet and exercise has been demonstrated to have cognitive and metabolic benefits (improved glucose and insulin metabolism) in adults with impaired glucose tolerance[151]. Dietary lifestyle changes can have a positive impact throughout the lifespan and appear to not only reduce the risk of acquiring cognitive impairments, but can also attenuate existing impairments. For example, a recent study showed that a 4-week low-saturated fat/low-glycaemic index diet resulted in improved memory performance and insulin metabolism in adults with amnestic mild cognitive impairment[168].

The rise in obesity, diabetes and metabolic syndrome in recent years highlights the need for targeted dietary and lifestyle strategies to promote healthy lifestyle and brain function across the lifespan and for future generations. The data indicate that modifiable lifestyle factors and most notably dietary changes may contribute significantly to optimal cognition across the lifespan. Consequently, the therapeutic effects of longer-term dietary intervention may be a promising avenue of exploration. Lifestyle changes are difficult to execute and to maintain, but present an exciting potential for optimizing cognitive performance across the lifespan.

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Figure 1: Nutrition and cognition: potential for optimizing cognitive performance across the lifespan